23565

IN THE U.S. PATENT AND TRADEMARK OFFICE

Inventor	Istvan EROS	
Patent App.	10/575,145	
Filed	23 March 2007	Conf. No. 9304
For	TRANSDERMAL PHARMACEUTICAL COMPOSITION	
Art Unit	1614	Examiner Lewis, A

Hon. Commissioner of Patents
Box 1450
Alexandria, VA 22313-1450

Appealed 13-Jul-09

APPEAL BRIEF UNDER 37 CFR 41.37

Now comes appellant by his duly authorized attorney and submits his brief under the provisions of 37 CFR 41.37.

I. REAL PARTY IN INTEREST

The real party in interest is Richter Gedeon Vegyeszeti Gyar Rt, a corporation organized under the laws of Hungary, having a principal place of business at Gyomroi ut 19 - 21, H-1103, Budapest, Hungary.

II. RELATED APPEALS AND INTERFERENCES

There are no prior or pending appeals, interferences or judicial proceedings known to Appellants or to the Appellants'

legal representative, which may be related to, directly affect, or be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF THE CLAIMS

Claims 1 through 70 have been canceled. Claims 71 through 100 are pending. Claims 80 through 86 have been rejected as obvious under 35 USC 103 in view of the cited prior art. Claims 71 through 79 and 87 through 100 have been withdrawn from further consideration as directed to a non-elected invention. Appellants are appealing the rejection of claims 80 through 86, and in the event that the Board reverses the Examiner's rejection of those claims, request that the Examiner broaden her search of the prior art to include the subject matter of claims 71 through 79 and 87 through 100.

IV. STATUS OF AMENDMENTS

Appellants failed to file a timely response to the final office action mailed 24 December 2008. Thus the present application has became abandoned as of 24 March 2009, the extendable due date set for response in the final office action of 24 December 2009. However, Appellants' failure to file a timely response to the outstanding final office action was unintentional,

and Appellants on 13 July 2009 have filed a Response Under 37 CFR 1.116 to the Final Office Action, along with a Petition for Revival Under 37 CFR 1.137(b), and a Notice of Appeal. At present the Petition for Revival is under review at the Office of the Commissioner.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Appellants have discovered a new liquid crystal gel compositions for transdermal administration containing both an aqueous component comprising water, ethanol, benzyl alcohol, and a hyaluronic acid salt or complex and a non-aqueous component comprising isopropyl myristate and which further contains polyoxyethylene-glyceryl-trioleate as surfactant and propylene glycol as a co-surfactant. See page 18, lines 4 through 19. Appellants have found that their new liquid crystal gel compositions do not suffer from the disadvantage of causing skin irritation, which is a common well-known problem with the prior art transdermal gel compositions that include only a non-aqueous component. See page 13, lines 24 through 30 of the present application. On page 14 of the present application, further advantages are listed for the presently claimed compositions, including the transparency of the present compositions on the skin, which creates a better appearance of the patient, and a much less

greasy appearance on the skin than the compositions that include only a non-aqueous component.

In addition Appellants point to the high storage stability of the presently claimed compositions, even after storage for two months, is evidenced by the test data in Figures 5 and 6 for estradiol and etonogestrel as the respective therapeutically active ingredients added to the liquid crystal gel as discussed on page 16 of the application, and as further discussed on pages 30 through 34 of the application and as further evidenced by the test data in Tables 1 through 4. The data in Figures 5 and 6 and in Tables 1 through 4 establish high storage stability for the new liquid crystal gels containing both an aqueous and a non-aqueous component as can be seen by the even release of the therapeutically active compound estradiol and in Figures 5 and 6 following administration of the therapeutically active compounds estradiol and etonogestrel.

A first feature of the invention is found in claim 86 directed to a transdermal pharmaceutical composition as a liquid crystal gel, which consists essentially of:

(a) at least one therapeutically active ingredient and

(b) a liquid crystal gel which contains the at least one therapeutically active ingredient, said liquid crystal gel consisting essentially of:

Polyoxyethylene-glyceryl-trioleate	26.7 - 40.0%,
Propylene-glycol	13.3 - 20.0%,
Isopropyl myristate	5.0 - 35.0%,
Ethanol	0.01 - 10.0%
Benzyl alcohol	0.5 - 1.5%,
a hyaluronic acid salt or complex	0.01 - 2.00%, and
Purified water	12.5 to 26.5%.

Antecedent basis for this feature of the invention may be found in the specification on page 14, lines 24 through 27, page 15, lines 1 through 4, and page 21, lines 27 to 30 through page 22. Appellants have found that their particular liquid crystal gel as defined herein containing both an oil phase and an aqueous phase comprising a hyaluronic acid salt or complex works surprisingly well in the transdermal administration of a multitude of therapeutically active compositions, which may be included in the gel. See page 15, lines 18 to 24 of the specification.

A second feature of the invention is found in claims 80 to 85 as follows:

A transdermal pharmaceutical composition as a liquid crystal gel, which consists essentially of:

(a) an estrogen component; and

(b) a progestin component, as therapeutically effective ingredients wherein said estrogen component and said progestin component are included in a therapeutically effective amount sufficient for hormone replacement therapy; and

(c) a liquid crystal gel which contains the therapeutically active ingredients, said liquid crystal gel consisting essentially of:

Polyoxyethylene-glyceryl-trioleate	26.7 - 40.0%,
Propylene-glycol	13.3 - 20.0%,
Isopropyl myristate	5.0 - 35.0%,
Ethanol	0.01 - 10.0%
Benzyl alcohol	0.5 - 1.5%,
a hyaluronic acid salt or complex	0.01 - 2.00%, and
Purified water	12.5 to 26.5%

Antecedent basis for this feature of the invention may be found in the specification on page 14, lines 20 to 23, page 15, lines 8 through 12, in Tables 1 through 4 on pages 30 to 34 of the specification, in Figures 5 and 6 and in the specific Examples 1 through 32. Here the Appellants have focused on liquid crystal gel pharmaceutical compositions containing as therapeutically active ingredients an estrogen compound and a progestin compound, such as estradiol and gestodene, or estradiol and etonogestrel, respectively. Appellants have particularly found surprising success in the transdermal administration of such compositions to

patients in need of hormone replacement therapy (HRT). See once again page 14, lines 20 through 24, the data in Tables 1 through 4, the data in Figures 5 and 6, and Examples 1 through 32.

VI. GROUNDS FOR REJECTION TO BE REVIEWED ON APPEAL

The principal issue to be determined in this appeal is whether claims 80 through 86 are obvious pursuant to 35 USC 103 in view of the combination of prior art references cited by the Examiner against those claims, namely, SZABO et al European Patent 509,761, in combination with US Patent Publication 2004/0192620 to BUNSCHOTEN et al, in further view of US Patent 5,326,566 to PARAB, in further view of BRYNHILDSEN et al, and in further view of US Patent 5,616,568 to POUYANI et al. See page 3, lines 10 through 16, and the discussion that follows through page 8 of the final office action.

In addition there are several sub-issues that require resolution in order to reach a conclusion concerning the principal issue raised above. Those sub-issues include the following:

1. Whether the only differences between the compositions disclosed in SZABO et al and in the presently claimed compositions on appeal are that the SZABO et al compositions do not include sodium or zinc hyaluronate salts or complexes, isopropyl myristate,

and with respect to claims 80 to 85, specific use of hormones as active ingredients, and in particular whether SZABO et al discloses oil-in-water emulsions in liquid crystal gel compositions. See page 4, lines 8 and 9, and page 7, lines 3 through 7 of the final office action.

2. Whether one "skilled in the art" would be motivated by the teachings in the POUYANI et al reference to include sodium or zinc hyaluronate salts or complexes in the presently claimed liquid crystal gel compositions. See the last six lines of page 5 and the first four lines of page 6 as well as the last four lines of page 7 of the final office action.

3. Whether the presently claimed transdermal pharmaceutical compositions as a liquid crystal gel are broad enough to include a transdermal patch even though there is not a single reference to a transdermal patch in the claims or in the specification. See page 8, lines 1 through 5 of the final office action.

VII. The Arguments

Claims 80 Through 86 are not Obvious in View of the Cited Combination of Prior Art References

At the outset the Examiner and Appellants have a significant difference in opinion over what EP 0 509 761 to SZABO et al discloses and over what the POUYANI et al discloses and how close the disclosure in these reference comes to the presently claimed invention. The Examiner admits on page 7, second full paragraph of the final office action, that SZABO et al does not disclose lyotropic liquid crystal gel compositions that contain either hyaluronic acid, sodium hyaluronate or zinc hyaluronate. In the first paragraph of page 10 of the preceding office action, the Examiner argued that the SZABO lyotropic liquid crystal compositions did contain hyaluronic acid. Since SZABO et al serves as the Examiner's chief reference in the combination of references applied against the claims, Appellants wish to go over every difference between the SZABO lyotropic liquid crystal compositions and those in the appealed claims 80 through 86.

The Appellants preferably use sodium hyaluronate or zinc hyaluronate as the hyaluronate salt or complex in the liquid crystal forming polymer. SZABO et al use PEG 35 000 and no salt or complex of hyaluronic acid. The Examiner has not provided any evidence that a hyaluronate salt or complex such as sodium hyaluronate or zinc hyaluronate is an art-recognized equivalent of PEG 35 000 and the fact that Appellants use the sodium or zinc hyaluronate in an aqueous system and SZABO et al uses the PEG 35

000 in an anhydrous system provides further evidence that the hyaluronates and the PEG 35 000 are not equivalent.

The Appellants in their elected species of claim 80 use an estrogen/progestin combination of hormone replacement drugs as the active ingredients whereas SZABO et al uses deprenyl, an MAO inhibitor as the active ingredient.

The Appellants' liquid crystal gel contains both a non-aqueous component and an aqueous component. The SZABO et al liquid crystal gel is anhydrous.

The Appellants liquid crystal gel specifically includes polyoxyethylene-glyceryl-trioleate as surfactant, which is not disclosed in the SZABO et al compositions.

The Appellants' compositions also include isopropyl myristate as a surfactant and this compound is not found in the SZABO et al compositions.

Appellants believe that the cited combination of the prior art references SZABO et al, BUNSCOHTEN et al, PARAB PV, BRYNHILDSEN et al, in further view of POUYANI et al provides no basis to reject any claim now presented as obvious under 35 USC 103 for the following reasons:

A. In the first full paragraph on page 7, the Examiner argues that SZABO et al discloses transdermal compositions containing both oil and water as well as anhydrous transdermal compositions. The Examiner points to page 2, lines 25 to 30 of SZABO et al. Appellants believe that the Examiner's citation of this passage is entirely misleading because this passage relates to the prior art cited in SZABO et al, which is a completely different composition from the anhydrous transdermal gel compositions disclosed in SZABO et al further down the page starting on line 32. The transdermal basic ointments disclosed in SZABO et al on page 2, line 25 are not lyotropic liquid crystal gel compositions and have nothing to do with lyotropic liquid crystal gel compositions. Thus Appellants maintain that the only lyotropic liquid crystalline gel compositions disclosed in SZABO et al are anhydrous.

B. Appellants believe that the fact that their presently claimed liquid crystal gel compositions contain water and that the liquid crystal gel compositions of SZABO et al specifically do not, is itself a highly significant difference. Not only has the Examiner failed to establish an art-recognized equivalence between aqueous and non-aqueous liquid crystal gel compositions but furthermore it is the Appellants' aqueous phase that includes the zinc or sodium hyaluronate salt or complex, which is soluble therein. There is no aqueous phase in the SZABO et al compositions

to solubilize the zinc or sodium hyaluronate salt or complex, so why would one "skilled in the art" even think to add zinc or sodium hyaluronate or any other hyaluronate salt or complex to the non-aqueous systems disclosed in SZABO et al?

C. In the presently claimed lyotropic liquid crystal gel compositions, Appellants use a hyaluronate salt or complex, such as sodium hyaluronate or zinc hyaluronate, whereas in SZABO et al the inventors specifically use Polyoxyethylene 35 000 or any similar polymer having a coilness characterizing a value of >0.6. Appellants emphasize that structurally this polymer is far removed from either sodium hyaluronate or zinc hyaluronate. Furthermore, Appellants see no reason that one "skilled in the art" would substitute sodium hyaluronate or zinc hyaluronate for the PEG 35 000 disclosed in SZABO et al.

In view of the above, Appellants believe that there are many differences between the presently claimed transdermal liquid crystal gel compositions and the transdermal compositions disclosed in SZABO et al, in addition to the fact that Appellants' transdermal compositions contain a salt or complex of hyaluronic acid and those of the reference do not, and so the answer to the sub-issue number 1, set forth hereinabove is that there are many bases for distinction between the presently claimed liquid crystal

gel compositions and those disclosed in SZABO et al.

D. The Examiner admits in the first full paragraph of page 4 of the final office action that SZABO et al does not disclose either zinc or sodium hyaluronate or hormones such as estrogen in the lyotropic liquid crystalline compositions therein. However, at the bottom of page 7 the Examiner re-asserts that she can correctly combine SZABO et al with BUNSCHOTEN et al because SZABO et al discloses lyotropic liquid crystalline compositions for transdermal administration of a pharmaceutically active agent, and BUNSCHOTEN et al discloses transdermal administration of estrogen and progestin hormones with hydrophilic polymers, such as polycarbophil and polyvinylpyrrolidine in a gel composition. However, there are two additional missing elements from the Examiner's argument: the disclosure of the gel compositions in BUNSCHOTEN et al makes no mention of lyotropic liquid crystalline compositions and makes no mention of either sodium hyaluronate or zinc hyaluronate, or any other hyaluronate salt or complex, which are structurally far removed from either polycarbophil and polyvinylpyrrolidine. In paragraph [0092] BUNSCHOTEN et al makes mention of hyaluronic acid per se to facilitate transmucosal administration of hormones. One again, however, there is no mention of sodium or zinc hyaluronate or any other hyaluronate salt or complex for any purpose, no mention of liquid crystal gel compositions, and no mention even of hyaluronic acid to facilitate

transdermal administration of hormones in the form of a liquid crystal gel. Thus Appellants maintain that the combination of SZABO et al and BUNSCHOTEN et al falls far short of suggesting the presently claimed invention.

E. The Examiner admits that none of the SZABO et al, BUNSCHOTEN et al, and PARAB references discloses sodium hyaluronate or zinc hyaluronate or any other hyaluronate salt or complex in the preparation of lyotropic liquid crystalline gel compositions for transdermal administration of estrogen/progestin hormones or of any other pharmaceutically active ingredients. However at the bottom of page 7 of the final office action, the Examiner argues that POUYANI et al discloses that the salt form of hyaluronic acid (HA) increases the ability of HA to be a good drug carrier. Appellants do not agree with the Examiner's interpretation of POUYANI et al. In the paragraph at the bottom of column 3 going onto column 4, the reference discusses the instability of hyaluronic acid. In the first paragraph in column 4 of the reference it is stated that hyaluronic acid naturally occurs in the form of its sodium salt. Nowhere does the reference disclose or suggest preparing liquid crystal gel compositions for transdermal administration of a pharmaceutically active ingredient. Nowhere does the reference say that the sodium salt of hyaluronic acid is a better form of hyaluronic acid to serve as a drug carrier than hyaluronic acid per se. In fact the whole point of POUYANI et al is to provide a more

stable form of hyaluronic acid by functionalizing the hyaluronic acid or sodium hyaluronate with dihydrazide. See column 4 of the reference. The fact remains that neither POUYANI et al nor any other prior art reference or combination of references discloses or suggests the preparation of a lyotropic liquid crystalline gel that comprises both an aqueous and an organic phase, or for that matter even discloses or suggests that a salt or complex of hyaluronic acid could be an ingredient in the aqueous phase of a lyotropic liquid crystalline gel.

F. Thus the Examiner misreads POUYANI et al when she states that the reference discloses that sodium hyaluronate is a better form of hyaluronic acid than HA per se to serve as a drug carrier and concludes that the reference discloses that hyaluronic acid or sodium hyaluronate per se (non-functionalized) would be stable enough to serve as a drug carrier. Column 4, lines 7 and 8 indicates only that hyaluronate often occurs naturally as the sodium salt, sodium hyaluronate, but does not say that sodium hyaluronate is more stable than hyaluronic acid. When the Examiner points out that POUYANI et al in column 3, lines 60 to 65 states that hyaluronate possesses a number of characteristics that make it advantageously used as a drug carrier, that it is biocompatible, non-immunogenic, subject to natural degradation by enzymes, and possesses OH, COOH, and CH_2OH groups that may be covalently modified, she reads only what she wants to read, and disregards the

rest that follows after line 65 of column 3, where POUYANI et al discusses the instability of hyaluronate and the need to modify it by functionalizing it with dihydrazide in order to increase stability. According to column 3, line 65 to column 4, line 2:

"However, hyaluronate is known to be unstable and undergoes degradation below a pH of about 2 and above about pH 9. The mild reaction conditions used in the invention avoid this degradation. Moreover, the modified products show improved resistance to pH extremes."

Thus POUYANI et al requires the functionalization to stabilize the hyaluronate so that the hyaluronate may serve as an adequately stable drug carrier and therefore discourages the use of salts or complexes of hyaluronic acid per se, without the functionalization, as drug carriers. In view of the above, Appellants believe that POUYANI et al does not provide motivation for the skilled worker in the art to include a salt or complex of hyaluronic acid, such as zinc or sodium hyaluronate in a liquid crystal gel transdermal pharmaceutical compositions and so the answer to sub-issue 2 should be that POUYANI et al does not provide the motivation necessary to modify the combination of SZABO et al, BUNSCHOTEN et al, and PARAB.

G. PARAB discloses only that a mixture of dibutyl adipate and isopropyl myristate is a good transdermal penetrant. There is no disclosure, however, of isopropyl myristate per se as a transdermal penetrant. Furthermore the fact that the combination of SZABO et al, BUNSCHOTEN et al and POUYANI et al is faulty is, by no means, cured by the citation of PARAB.

H. The BRYNHILDSEN et al reference relates to a transdermal patch and not to a lyotropic liquid crystal gel according to the present invention. Appellants disagree with the Examiner's statement at the top of page 8 of the final office action that the present claims, while directed to a transdermal liquid crystalline gel, do not avoid a transdermal patch. In the prior art there is a sharp distinction between a transdermal patch and a transdermal gel as transdermal delivery systems for a pharmaceutical. See paragraph [0091] of BUNSCHOTEN et al which draws a clear distinction between patches and gels as transdermal delivery system for pharmaceuticals. Thus Appellants strongly believe that the sub-issue number 3 should be clearly resolved in Appellants' favor, namely, that there is a distinction between compositions for transdermal administration that include a patch and compositions for transdermal administration in the form of a gel.

Now that Appellants have set forth their arguments to resolve each of sub-issues 1,2 and 3, Appellants believe that the principal issue in this appeal should be resolved in the Appellants' favor, that is the combination of prior art references cited by the Examiner against those claims, namely, SZABO et al European Patent 509,761, US Patent Publication 2004/0192620 to BUNSCHOTEN et al, in further view of US Patent 5,326,566 to PARAB, in further view of BRYNHILDSEN et al, and in further view of US Patent 5,616,568 to POUYANI et al, provides no basis for the obviousness of the presently claimed invention.

Appellants believe that all of the arguments set forth herein above, relate to the rejection of claims 80 through 86. However, the arguments relate especially to claims 80 through 85 because in those claims Appellants have limited the pharmaceutically active ingredients to an estrogen component and a progestin component. Thus claims 80 through 85 are even further removed from the SZABO et al reference which discloses the transdermal administration of a monoamine oxidase inhibitor through an anhydrous transdermal administration.

In view of the above, Appellants believe that the Examiner has failed to provide a basis for the rejection of any of the examined claims 80 through 86 as obvious in view of the cited prior art. Therefore the Appellants ask that the Board of Appeals

and Interferences to reverse the rejection of all claims under 365 USC 103 as obvious.

Appellants are charging the costs of filing this appeal brief to the credit card of the undersigned attorneys.

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VIII. CLAIMS APPENDIX

80. A transdermal pharmaceutical composition as a liquid crystal gel, which consists essentially of:

(a) an estrogen component; and

(b) a progestin component, as therapeutically effective ingredients wherein said estrogen component and said progestin component are included in a therapeutically effective amount sufficient for hormone replacement therapy; and

(c) a liquid crystal gel which contains the therapeutically active ingredients, said liquid crystal gel consisting essentially of:

Polyoxyethylene-glyceryl-trioleate	26.7 - 40.0%,
Propylene-glycol	13.3 - 20.0%,
Isopropyl myristate	5.0 - 35.0%,
Ethanol	0.01 - 10.0%
Benzyl alcohol	0.5 - 1.5%,
a hyaluronic acid salt or complex	0.01 - 2.00%, and
Purified water	12.5 to 26.5%

81. The transdermal pharmaceutical composition as a liquid crystal gel defined in claim 80 wherein the estrogen component is estradiol.

82. The transdermal pharmaceutical composition as a liquid crystal gel defined in claim 80 wherein the progestin compound is gestodene.

83. The transdermal pharmaceutical composition as a liquid crystal gel defined in claim 80 wherein the progestin compound is etonogestrel.

84. The transdermal pharmaceutical composition as a liquid crystal gel defined in claim 80 wherein the progestin compound is levonorgestrel.

85. A method of treating a patient for moderate to severe vasomotor symptoms, as well as hot flashes, nocturnal sweating, and palpitation due to post-menopausal estrogen deficiency, which comprises the step of transdermally administering to the skin of the patient, a therapeutically effective amount of the transdermal pharmaceutical composition defined in claim 80.

86. A transdermal pharmaceutical composition as a liquid crystal gel, which consists essentially of:

(a) at least one therapeutically active ingredient and

(b) a liquid crystal gel which contains the at least one therapeutically active ingredient, said liquid crystal gel consisting essentially of:

Polyoxyethylene-glyceryl-trioleate	26.7 - 40.0%,
Propylene-glycol	13.3 - 20.0%,
Isopropyl myristate	5.0 - 35.0%,
Ethanol	0.01 - 10.0%
Benzyl alcohol	0.5 - 1.5%,
a hyaluronic acid salt or complex	0.01 - 2.00%, and
Purified water	12.5 to 26.5%.

IX. IX EVIDENCE APPENDIX

Appellants have not introduced into evidence any materials that should be listed in this appendix.

X. RELATED PROCEEDINGS APPENDIX

There have been no decisions rendered by a court or by the Board of Appeals and Interferences in a related proceeding and no such proceeding has been identified in the Related Appeals and Interference Section of the Appeal Brief.